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2 EMA/CHMP/QWP/558185/2014
3 Committee for Medicinal Products for Human use (CHMP)

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5 **Concept paper on the development of a guideline on**
6 **quality and equivalence of topical products**

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Draft agreed by Quality Working Party	December 2014
Adopted by CHMP for release for consultation	26 February 2015
Start of public consultation	22 April 2015
End of consultation (deadline for comments)	22 July 2015

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Comments should be provided using this [template](#). The completed comments form should be sent to QWP@ema.europa.eu

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Keywords	Therapeutic equivalence, bioequivalence, pharmaceutical equivalence, generic and hybrid medicinal products, locally applied, locally acting products, topical products, dermatological use, <i>in vitro</i> , quality, CHMP
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14 **Problem Statement**

15 Topical products are exemplified by medicines for cutaneous use; but in broadest scope, they are
16 locally applied, locally acting products. They can be applied to any of the diverse external surfaces of
17 the body that may present a physiological barrier to drug absorption e.g. skin, eye, ear.

18 The site of local action for topical products may be:

- 19 • External - on the surface of the physiological barrier;
- 20 • Internal - at and about the physiological barrier; and
- 21 • Regional - beyond the physiological barrier in adjacent tissues.

22 The bioavailability of the active substance at the site of action from topical products is known to be
23 affected by the active substance's physicochemical properties, the topical formulation design, the
24 manufacturing process and the means and patient preference of dose administration. In addition, it is
25 known that the vehicle itself may influence the condition to be treated e.g. moisturisers and emollients.

26 For topical products, small changes in formulation, dosage form, administration or manufacturing
27 process may significantly influence the efficacy and/or safety and this presents challenges to the
28 prediction of therapeutic equivalence at time of marketing authorisation application and during
29 management of variations to marketing authorisations after approval.

30 Clinical trials are in principle necessary to demonstrate therapeutic equivalence, but other models may
31 be used, if adequately validated¹. In many cases, these other models have exhibited poor accuracy,
32 sensitivity, reproducibility, *in vitro in vivo* correlation and have been unable to provide convincing
33 evidence to predict therapeutic equivalence.

34 **1. Discussion (on the Problem Statement)**

35 **Quality of Topical Products**

36 In recent years, the assessment of topical products has evolved. It has become evident that their
37 quality needs to be thoroughly understood and characterised, supported by a robust manufacturing
38 process and control strategy. In addition, the designated shelf life needs to be based not only on
39 physical, chemical and microbiological stability, but also, when necessary, on evidence of stable *in vitro*
40 performance to assure equivalence throughout storage.

41 Sound product development is necessary to characterise and achieve adequate product quality;
42 reference to clinical studies to justify inadequate product development or poor product quality should
43 be avoided.

44 **Equivalence of Topical Products**

45 At present, for most topical products, demonstration of pharmaceutical equivalence is normally not
46 sufficient to predict therapeutic equivalence. However, a waiver of the need to provide therapeutic
47 equivalence data may be acceptable in the case of solutions, e.g. eye drop solutions, nasal spray
48 solutions or cutaneous solutions².

49 Extension of this waiver to other pharmaceutical forms may be possible, if based on an extended
50 concept of pharmaceutical equivalence combined with additional measures of equivalence, using

51 suitable *in vitro* and *in vivo* models and methods, and evidence of equivalence with respect to the
52 method and means of administration.

53 An extended concept of pharmaceutical equivalence could be developed based on appropriate
54 comparative quality data with the relevant reference medicinal product, including qualitative and
55 quantitative composition, microstructure, physical properties, product performance and administration.
56 The comparative data need to be representative, the test methods appropriate and validated, and
57 equivalence acceptance criteria adequate.

58 The additional measures of equivalence currently available include *in vitro* drug release through an
59 artificial membrane and / or human skin membrane to determine the rate and extent of drug release
60 or permeation, *in vivo* tape stripping to determine dermatopharmacokinetics and possibly
61 microdialysis. Furthermore, when drug absorption to the blood compartment from the site of
62 application is sufficiently high, then comparative pharmacokinetic studies should be supportive of
63 equivalence. Other methods might also be valid for some specific medicinal products.

64 The scientific rationale as to how these methods may be used to support a claim of therapeutic
65 equivalence needs to be developed, taking account of the site of action of the active substance(s). The
66 advantages and disadvantages of each method need to be considered. Method limitations may be
67 addressed by employing a battery of different techniques, but, in any case, this needs to be fully
68 explored and understood to avoid inappropriate use and claims.

69 Method variability, sensitivity and discrimination power also need to be addressed. It is acknowledged
70 that some methods may show some inherent variability, e.g. skin used in permeation studies, but
71 variability can also be due to poor conduct and inadequate validation. All studies should follow best
72 practice and quality assurance principles, which should be established and described.

73 In addition, possible limitations of this approach e.g. products with narrow therapeutic index and / or
74 significant systemic side-effects, and safety requirements, including local tolerance studies, should be
75 considered in the guideline.

76 Bioequivalence is generally not a suitable way to show therapeutic equivalence for topical products¹,
77 due to limited systemic bioavailability. When studies are needed to demonstrate therapeutic
78 equivalence, a topical medicinal product, developed to be pharmaceutically and therapeutically
79 equivalent to an innovator product should be submitted as a "hybrid medicinal product"³.

80 The guideline will aim to develop a systematic approach to describe methods or combinations of
81 methods for the prediction of therapeutic equivalence, when taken with evidence of extended
82 pharmaceutical equivalence.

83 **2. Recommendation**

84 The scope of the guidance should focus on locally acting, locally applied products for cutaneous use,
85 and other routes, if possible and appropriate.

86 The new guideline should address the quality requirements of topical products, containing new or
87 known active substances, throughout their marketing life.

88 The concept of pharmaceutical equivalence for topical products should be developed and extended to
89 include e.g. qualitative and quantitative equivalence of formulation, physical properties and
90 microstructure, administration and *in vitro* drug release properties.

91 Guidance on alternative *in vitro* and *in vivo* methods that characterise the bioavailability of the active
92 substance to the local site of action should be developed.

93 The guideline should consider the application of an extended pharmaceutical equivalence with
94 alternative *in vitro* and *in vivo* models and methods to predict therapeutic equivalence with reference
95 medicinal products, *in lieu* of therapeutic equivalence studies in patients.

96 **3. Proposed Timetable**

97 The Concept Paper will be released for 3 months external consultation.

98 Following the receipt of Concept Paper comments, the draft Guideline will be prepared and released for
99 6 months external consultation.

100 The draft Guideline will be revised in light of comments received, finalised and published.

101 **4. Resource requirements for preparation**

102 The preparation will mainly involve the Quality Working Party (QWP), with support from other Working
103 Parties and expertise from academia, as necessary.

104 **5. Impact assessment (anticipated)**

105 The new guideline will provide guidance for pharmaceutical industry and regulatory authorities that is
106 in line with current knowledge.

107 **6. Interested Parties**

108 Academia, international scientific societies, pharmaceutical industry

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111 **7. References to literature, guidelines, etc.**

- 112 1. Note for Guidance on the clinical requirements for locally applied, locally acting products
113 containing known constituents CPMP/EWP/239/95;
- 114 2. Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **
115 Appendix II, Locally acting and locally applied products).
- 116 3. Notice to Applicants, Revision 4, Volume 2A, Procedures for Marketing Authorisation, Chapter 1,
117 Marketing Authorisation, June 2013, Chapter 5.3.2.2, Application in accordance with paragraph 3
118 of Article 10 ("hybrid "medicinal product);